

Draft Guidance for Industry and FDA Staff

Clinical Study Designs for Surgical Ablation Devices for Treatment of Atrial Fibrillation

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

**Cardiac Electrophysiology and Monitoring Branch
Division of Cardiovascular Devices
Office of Device Evaluation**

Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This draft guidance provides FDA's proposed recommendations on clinical trial designs for surgical ablation devices intended for the treatment of atrial fibrillation (AF). The recommendations in this guidance address clinical studies for new surgical ablation devices intended for treatment of AF, as well as for legally marketed surgical ablation devices for which a new indication for treatment of AF is sought.

Atrial fibrillation is a complex arrhythmia and its precise mechanisms remain unclear. Current treatments span a spectrum of non-invasive to highly invasive options and include medical and surgical variants. The success of the MAZE procedure¹ and its successors has led to the development of surgical ablation devices designed to mark cardiac tissue in a manner similar to suture lines, thereby disrupting the path of the electrical impulses causing the patient's AF.

¹ Cox JL, Schuessler RB, d'Agostino Jr HJ et al; The surgical treatment of atrial fibrillation III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991;101:569-583.

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We believe that several important elements of appropriate clinical study design – such as inclusion and exclusion criteria and assessment of effectiveness – differ for patients with longstanding persistent AF and patients with symptomatic paroxysmal AF. This guidance addresses those differences.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to clinical study designs for surgical treatment of atrial fibrillation and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

2. Scope

This draft guidance document addresses clinical study design issues associated with devices intended for surgical ablation, under direct visualization, for the treatment for AF as a rhythm disturbance. See the “Terminology” section below for a distinction between “AF as a rhythm disturbance” and “AF as a disease.”

The scope of this guidance document specifically excludes cardiac ablation devices not intended for use under direct visualization and cardiac ablation devices delivered intravascularly.

The following table outlines additional device types excluded from the scope of this guidance:

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Classification Regulation (21 CFR)	Class	Product Code	Description
878.4350	II	GEH	Cryosurgical unit and accessories
878.4400	II	GEI	Electrosurgical cutting and coagulation devices and accessories
		NEY	Microwave ablation system and accessories
		NTB	Ultrasound ablation system and accessories
		OAB	Low energy direct current thermal ablation system
		OCL	Surgical device for ablation of cardiac tissue
878.4810	II	GEX	Powered surgical laser instrument
none (post-Amendments)	III	LPB	Cardiac ablation percutaneous catheter
none (post-Amendments)	III	OAD	Cardiac ablation percutaneous catheter for treatment of atrial flutter
none (post-Amendments)	III	OAE	Percutaneous catheter intended for treatment of atrial fibrillation

FDA believes that the devices addressed by this guidance document are significant risk devices as defined in Title 21, Code of Federal Regulations (CFR) 812.3(m).² In addition to having to comply with the regulations governing institutional review boards (IRBs) (21 CFR part 56) and informed consent (21 CFR part 50), sponsors of such studies must obtain FDA and IRB approval of their application for an investigational device exemption (IDE) before they may begin any study on an investigational device (see section 520(g) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 360j(g); 21 CFR 812.42).

3. Terminology

The following terms are defined as described for the purposes of this guidance document.

² See also

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/UCM118082.pdf>.

A. Surgery or Surgical Approach

We define surgery or the surgical approach as a clinical procedure carried out under direct visualization. This means that the clinician is able to see, either directly or by means of live video, the point or area of contact between the ablating device and the cardiac tissue. Included in this definition is open-chest surgery and minimally invasive surgery via thoracoscopy, as long as the clinician can visualize the ablation procedure adequately. Specifically excluded from this definition are clinical procedures that are performed principally under indirect visualization, such as cardiac catheterization, or approaches to the epicardium via pericardial access carried out under fluoroscopic or echocardiographic guidance. The guidance document entitled *Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation - Guidance for Industry and FDA Staff* addresses study design for catheter ablation as a therapy for AF.³

B. Paroxysmal, Persistent, and Longstanding Persistent AF

The table below summarizes the FDA’s definition of different classifications of atrial fibrillation, as applied in this guidance document:

Classification	Definitions
Paroxysmal	recurrent AF (>2 episodes) that terminates spontaneously within seven days
Persistent	AF which is sustained beyond seven days, or lasting less than seven days but necessitating pharmacologic or electrical cardioversion
Longstanding Persistent	continuous AF of greater than one-year duration
Permanent	patients where a decision has been made not to pursue restoration of sinus rhythm by any means

The above terms “paroxysmal,” “persistent,” and “longstanding persistent” AF as used in this guidance are adopted from the HRS/EHRA/ECAS Expert Consensus

³ See

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072590.htm>

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Statement on Catheter and Surgical Ablation of Atrial Fibrillation.⁴ Paroxysmal AF is by nature episodic and can occur in clusters with temporal gaps between recurrences. This makes the evaluation of the effectiveness of a therapy for paroxysmal AF more difficult than for persistent and longstanding persistent AF. FDA believes that in addition to the above definition for longstanding persistent AF, patients who have failed cardioversion may also be considered to have longstanding persistent AF depending on the definition used for failed cardioversion.

C. AF as a Rhythm Disturbance versus AF as a Disease

AF as a rhythm disturbance should be distinguished from AF as a disease. AF as a rhythm disturbance refers solely to the presence of AF as diagnosed with appropriate electrocardiographic techniques. AF as a disease additionally refers to the functional characteristics caused by an AF rhythm. We refer to “termination of AF” as an outcome of treating AF as a rhythm disturbance, and “cure of AF” as an outcome of treating AF as a disease.⁵

4. Study Design

FDA recognizes that there is no unique “best design” for clinical investigations of devices. However, the elements discussed in this document embody FDA’s current thinking regarding appropriate study designs for these devices. The design, execution, and analysis of any clinical trial of a device should be appropriate to develop valid scientific evidence to substantiate the safety and effectiveness of the device for its intended use and patient population. (See 21 CFR 860.7.)

A. Randomized Controlled Trials

FDA believes that, in general, randomized controlled trials (RCTs) provide the least burdensome means of developing valid scientific evidence for surgical ablation devices intended for the treatment of AF. Potential advantages to randomized controlled trial designs extend to evaluation of both device effectiveness and device safety. Randomization also provides a sound basis for statistical inference.

Assurance that subject populations are similar in test and control groups is best attained by randomly dividing a single sample population into groups that receive the

⁴ Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up. *Heart Rhythm* 2007;4(6):816-61.

⁵ Please note that the recommendations in this guidance do not apply to those devices seeking an indication of cure of AF as a disease.

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test treatment (i.e., ablation) or control treatment (i.e., no ablation). This technique avoids systematic differences between groups with respect to known or unknown baseline variables that could affect safety and/or effectiveness outcomes. Variables that may affect the safety profile (adverse event rates) include patient characteristics, concomitant cardiopulmonary disease, device design, evolving procedural methods, and operator experience. Inability to eliminate systematic differences between treatment groups is a major problem of studies without a concurrent randomized control.

If you conduct a randomized control trial, we recommend that you select an appropriate control therapy or control group. Whether a particular control is appropriate depends on:

- The specific indication for use under study
- Your intended target patient population
- The design of your device
- Your assessment of potential confounding factors
- Any concomitant surgical procedures.

B. Alternative Study Designs

Although we generally recommend RCTs, we understand the difficulty of enrolling this particular patient population in this type of trial, and we will consider alternative study designs. However, any study design should be scientifically sound and address relevant safety and effectiveness questions. Thus, to the extent that your alternative study design departs from the RCT design, we recommend you employ rigorous methodology designed to reduce potential sources of bias and other confounders. We also recommend that you thoroughly explain the scientific rationale supporting your design in your IDE submission. We note that if FDA finds that there is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or that the investigation is scientifically unsound, FDA may disapprove an IDE application. (See 21 CFR 812.30(b)(4).)

Non-Randomized Concurrent Controls

A non-randomized concurrent control design is one alternative to a randomized controlled study. Such a study would compare data from subjects receiving ablation treatment from the investigational device to data from subjects either receiving no ablation treatment or receiving an alternative treatment. (See 21 CFR 860.7(f)(iv)(a), (c).) However, the comparability of the treatment and control groups may be reduced because the benefits of randomization are eliminated in such a study. Potential limitations on comparability include differences in patient

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care across investigational sites and factors that may introduce selection bias such as concomitant underlying disease and differences in AF disease. Thus, non-randomized studies should include rigorous steps to closely match subjects in the control group with subjects in the treatment group. Either covariate analysis or propensity score analysis can enhance the comparability of the treatment and control arms of your study. We recommend that you prospectively describe in detail any methods of analysis in your clinical protocol.

Historical Controls

FDA will consider a study design implementing an historical control that compares data from a group of subjects receiving the test treatment with historical data from a group of comparable patients external to the study who received no ablation treatment, but who followed an established effective regimen at an earlier time. (See 21 CFR 860.7(f)(1)(iv)(d).) FDA believes that if an historical control is employed, a thorough analysis of the relevant medical literature should be provided in support of your historical control choice. We recognize that, due to the heterogeneity of disease presentation and treatment in the target AF patient population and the variety of ablation, drug, and other therapies that may be used for treatment of AF, the use of an historical control may complicate the collection and analysis of appropriate medical literature. Whenever possible, FDA recommends you use a control cohort for which patient-level data are available. In lieu of this, if patient-level data are not available, FDA recommends that you propose a performance goal supported by a thorough analysis of the relevant medical literature.

C. Control Group Considerations

If your study utilizes a randomized or non-randomized concurrent or historical control arm, appropriate potential concurrent control therapies may include:

- best medical therapy with antiarrhythmic drugs
- ablation therapy with one or more medical devices indicated for the treatment of atrial fibrillation

Regardless of the concurrent control arm selected, several strategies may be appropriate to facilitate subject recruitment. Appropriate strategies may include use of 2:1 or other randomization allocation ratios, and selection of a control arm with therapy by best medical management instead of no therapy.

If you elect to use best medical therapy with antiarrhythmic drugs as the control therapy for evaluation of effectiveness, FDA recognizes that drug regimens are tailored to individual circumstances and that no unique optimal regimen exists.

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However, FDA recommends that any investigation with antiarrhythmic drugs utilize a pre-specified tiered protocol that delineates criteria for initial drug selection and for changes in drug therapy.

If your study design includes an historical control, we recommend you choose a control cohort with characteristics that will maximize the likelihood that your study outcomes will be interpretable, such as:

- patient level data is available for control group
- ablation lesion set for control group is known
- duration, method, and rigor of follow-up in study subjects is known
- surgical approach in control group is equivalent to that in study subjects
- AF disease and underlying heart disease in control group and study subjects is similar
- concomitant procedures in control group and study subjects are the same.

D. Ablation Procedure Lesion Sets

We recognize that there may not be one set of ablation lesions or ablation lines that are generally accepted as being the most effective in treating atrial fibrillation. However, we recommend that, to the extent possible, all subjects enrolled in your study have the same set of ablation lesions performed. Any deviations from the protocol-specified lesion set should be clearly documented in the case report forms.

E. Concomitant Surgery versus Surgery for Lone AF

AF ablation performed concomitantly with another surgical procedure has a different risk-benefit profile than surgery done solely for the purpose of performing AF ablation. When surgical AF ablation is an adjunctive procedure in a patient already indicated for cardiac surgery, the additional risk posed by the ablation procedure may be small compared to the risks of the primary surgical procedure. When the sole purpose of the surgery is to perform AF ablation, FDA intends to weigh the risk of the surgery and ablation procedure against the sole possible benefit of treatment of AF. In your IDE application for a trial where the only purpose of the surgical procedure is ablation for treatment of AF, you should provide a sound scientific rationale to support your hypothesis that the benefits of AF ablation outweigh the risks of the surgical procedure. (See 21 CFR 812.30(b)(4).) In this situation, the careful selection of the control population is particularly important to FDA's evaluation of your trial design and the study results.

5. Indications for Use

We recommend that your study design reflect the proposed intended use and indications for use of your ablation device. We believe that your proposed indications for use should identify factors that may affect the risk/benefit profile of your device, such as the type of AF treated, the surgical approach used, any concomitant procedures, and relevant patient characteristics. Specific aspects of the study design often limit the indications for use of a device. For example, if your study includes only subjects with longstanding persistent AF, the corresponding indications for use may be limited to termination of longstanding persistent AF. If your study design pertains only to ablation concomitant with mitral valve replacement or repair surgery, approval of your device may be limited to that specific indication. If the only surgical procedure used in your study employs a minimally invasive surgical approach, your indications may be limited accordingly.

Other Indications

Surgical ablation devices have a range of potential indications beyond treatment of AF as a rhythm disturbance. These other indications include improvement in atrial transport, improved ventricular function, reduced risk of stroke, and reduced risk of heart failure. However, FDA is not aware of any direct clinical evidence that termination of AF following surgical AF ablation results in any of these patient benefits. Therefore, FDA does not consider termination of AF to be an appropriate surrogate indicator for these benefits. As a result we recommend that clinical studies directly measure and support any indications beyond treatment of AF as a rhythm disturbance. For example, a study that demonstrates restoration of atrial contraction, in addition to effective termination of AF, may support indications that include improved atrial function. Similarly, a study that demonstrates increased left ventricular ejection fraction and improvement in ventricular dimensions may support an indication for restoration or maintenance of ventricular function.

Indications that include reduction in the risk of stroke should be supported by a study designed to evaluate the risk of stroke either while continuing or following termination of anticoagulation therapy.

In summary, you should formulate the indications for use for which you plan to seek approval in concert with clinical trial hypotheses that will support the indications for use.

6. Study Endpoints

FDA believes that clinical studies involving subjects with paroxysmal AF, studies involving subjects with persistent AF, and studies involving longstanding persistent AF subjects are likely to be different in terms of procedural complexity as well as ease of

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follow-up. Clinical studies involving these subjects may also differ in terms of appropriate effectiveness endpoints, and in terms of appropriate inclusion and exclusion criteria. Where appropriate, the recommendations in this guidance address studies on treatment of paroxysmal AF, persistent AF, and longstanding persistent AF separately.

A. Primary Effectiveness Evaluation

We recommend that you demonstrate that the benefit to subjects from the therapy is both clinically meaningful and statistically significant relative to the increased risk associated with the use of the ablative device. We generally recommend you evaluate the primary effectiveness in the absence of antiarrhythmic drug therapy. However, an outcome evaluated in the presence of an antiarrhythmic drug that was not effective in treating AF prior to enrollment in the study of the surgical ablation device may serve as a primary or secondary effectiveness endpoint. In either case, you should justify your choice of effectiveness endpoint.

Longstanding Persistent and Persistent AF: Primary Effectiveness Endpoint

For the primary effectiveness endpoint, FDA recommends freedom from AF through six months for longstanding persistent patients and freedom from AF through nine months for persistent patients. The rationale for this difference is related to the ability to more definitively assess freedom from AF for longstanding persistent AF in a shorter period of time, given its predominantly continuous nature prior to ablation.

Your assessment of effectiveness of the device should include a measure of acute procedural effectiveness, such as electrical isolation of the pulmonary veins. You should prospectively define in detail the means by which you will evaluate AF recurrence and scenarios indicative of treatment failure (e.g., AF recurrence, left atrial flutter, left atrial tachycardia). However, we do not believe there is an acute efficacy endpoint for surgical therapy for AF that is appropriate as a surrogate for the recommended primary efficacy endpoint. Generally, we recommend periodic Holter monitoring as the preferred modality for assessing effectiveness, although other modalities, such as resting electrocardiograph (ECG) recording, loop recorders, and event monitoring may be adequate. We believe that less direct evaluation modalities, such as reduction in perceived symptoms, are not able to demonstrate primary effectiveness due to the subjective nature of such modalities and the potential for placebo effect. We believe that the primary effectiveness endpoint for a rhythm disturbance is AF termination (without iatrogenic arrhythmias) and not necessarily the resumption of normal sinus rhythm.

Paroxysmal AF: Primary Effectiveness Endpoint

For paroxysmal AF, FDA recommends freedom from AF for one year as the primary endpoint. We believe this follow-up period minimizes the confounding effects of a clustered, non-random AF recurrence pattern. You should prospectively define in detail the means by which you evaluate AF recurrence and scenarios indicative of treatment failure (e.g., AF recurrence, left atrial flutter, left atrial tachycardia). Generally, we recommend periodic electrocardiographic monitoring as the preferred modality for assessing effectiveness. It is possible that subjects may experience paroxysms of AF outside of the scheduled electrocardiographic monitoring periods. We therefore recommend that throughout the follow-up period an event monitor, Holter monitor, or other device be made available to any study subject who experiences symptoms indicative of AF. We further recommend that the protocol describe a plan to assess and ensure patient compliance with the periodic monitoring.

We also recommend that you explain the means by which your study design minimizes confounding factors, such as the placebo effect. We believe reduction in paroxysmal AF burden or recurrence is not an optimal primary endpoint because of the difficulty in determining the percent reduction that would be considered clinically significant in terms of patient benefit.

B. Secondary Effectiveness Endpoints

Depending on the design of the device and its indications for use, appropriate secondary effectiveness endpoints may include:

- AF burden
- improvement in symptom scores tracking dyspnea, dizziness, or palpitation
- improvement in quality of life
- improvement in exercise tolerance
- improvement in ventricular ejection fraction
- improvement in atrial transport
- atrial remodeling, by decrease in atrial size.

If you intend to present comparisons between groups for a secondary effectiveness endpoint in your labeling, your protocol should include a prespecified hypothesis and an adjustment for multiplicity, as appropriate. Your sample size estimation should take this secondary endpoint hypothesis into account. For secondary endpoints subject to placebo effect, such as exercise tolerance, quality of life, and symptom scores, we recommend that you design your study to minimize the placebo effect.

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Atrial Function

Assessment of the return of atrial function following AF ablation has been reported in the literature, and restoration of atrial transport has been cited as a benefit of the surgical MAZE procedure⁶ as well as surgical ablation for isolation of the pulmonary veins for treatment of AF.⁷ To date, however, clinical trials have focused almost exclusively on elimination of the rhythm disturbance. FDA believes that recovery of atrial function may have a positive impact on quality of life and on reduction of the risks associated with AF such as stroke and heart failure. If you intend to assess atrial function as part of the study, you should consider coupling this assessment with evaluation of risk reduction and improvement in quality of life. For example, see the scoring method for evaluating and reporting the return of atrial function proposed by Melo et al.⁸

Ventricular Function

Termination of the rhythm disturbance and the associated erratic and elevated ventricular rates may result in improvement in ventricular function. If you plan to assess ventricular function, your study design should include some means for evaluating ventricular function and dimensions, both pre- and post-procedure. This may include echocardiographic or other imaging evaluations of ventricular dimensions and ejection fraction coincident with assessment of rhythm state at the effectiveness evaluation.

C. Primary Safety Evaluation

FDA recommends a composite safety endpoint consisting of serious adverse events including, but not limited to:

- all-cause death
- stroke and transient ischemic attack (TIA)
- myocardial infarction (MI)
- thromboembolic events (pulmonary embolism and peripheral embolism)

⁶ Yuda S, Nakatani S, Kosakai Y, et al. Long-term follow-up of atrial contraction after the maze procedure in patients with mitral valve disease. *J Am Coll Cardiol* 2001;37(6):1622-7.

⁷ Thomas L, Boyd A, Thomas SP, et al. Atrial structural remodeling and restoration of atrial contraction after linear ablation for atrial fibrillation. *Eur Heart J* 2003;24(21):1942-51.

⁸ Melo JQ, Neves J, Adragao P et al. When and how to report results of surgery on atrial fibrillation. *Eur J Cardiothorac Surg*. 1997;12(5):739-44.

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- excessive bleeding
- deep sternal wound infection/mediastinitis
- damage to the specialized conduction system requiring permanent pacemaker
- damage to peripheral structures, such as the esophagus
- pulmonary vein (PV) stenosis.

In terms of safety and evaluation of adverse events, the investigational plan must include a description and analysis of all increased risks to which subjects will be exposed by the investigation. (21 CFR 812.25(c).) The sponsor must immediately conduct an evaluation of any unanticipated adverse device effect (UADE) (21 CFR 812.46(b)), and ensure that any reviewing IRB and FDA are promptly informed of significant new information about an investigation (21 CFR 812.40). If the sponsor determines that a UADE presents an unreasonable risk to subjects, the sponsor must terminate all investigations presenting such risk as soon as possible, and not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the UADE (21 CFR 812.46(b)(2)).

FDA believes that a one year follow-up for safety evaluation provides sufficient time to evaluate adverse events such as PV stenosis that may be manifested or progressive only at late time points in some subjects. A shorter follow-up period, e.g., less than one year, may be appropriate if using your device under direct visualization does not pose a risk of PV stenosis. If you believe this is the case, you should provide a sound rationale for follow-up duration of less than one year.

Pulmonary Vein Stenosis

When PV stenosis is identified as a risk associated with your device, we recommend that you evaluate PV stenosis using a baseline imaging study (CT or MRI), followed by an assessment using the same method at thirty days and six months post-procedure to evaluate stenosis progression. If subjects show evidence of PV stenosis at six months, we recommend additional follow-up imaging at twelve months post-procedure.

We recommend that you identify in the clinical protocol the extent of PV stenosis that you define as clinically significant as a percentage relative to baseline. You should explain why you believe the extent of PV stenosis you have identified is clinically significant. We also recommend that an independent, masked observer in a central core laboratory perform all evaluations of the imaging studies done to evaluate PV stenosis.

Case Report Forms should include a means for determining whether subjects are experiencing symptoms suggestive of PV stenosis.

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We believe subjects in a control arm who are not undergoing ablation are unlikely to experience PV stenosis and therefore need not be evaluated by imaging. A study using a surgical ablation procedure that involves direct visualization of the ablation device when used in the vicinity of the pulmonary veins need not include assessment of PV stenosis. If you determine that the risk of PV stenosis is minimal and therefore reason that PV assessment is not warranted in your study, we recommend that you describe how you made this determination and provide a scientific rationale in support of your reasoning.

7. Study Groups

FDA recommends that your study include patient populations in which the proposed therapy is most likely to show benefit. Selection of study subjects should carefully balance inclusion of subjects with characteristics needed to support a broad indication with exclusion of subjects to control for potential confounding factors. We recommend that your protocol list inclusion and exclusion criteria to define precisely the patient population likely to benefit from the proposed therapy.

The selected inclusion and exclusion criteria should ensure that subjects have a type of AF (i.e., paroxysmal, persistent, or longstanding persistent) that is consistent with the device's proposed indication for use. For proposed indications for longstanding persistent AF therapy, we recommend that the study include subjects with continuous AF as defined by the HRS/EHRA/ECAS Expert Consensus Statement who have failed standard medical therapy or in whom such therapy is contraindicated or not tolerated. For proposed indications for persistent AF therapy, we recommend that the study include subjects with at least two documented episodes of AF that were successfully cardioverted. For proposed indications for paroxysmal AF therapy, we recommend that the treatment arm include subjects with multiple documented episodes of highly symptomatic self-terminating AF.

Consistent with ACC/AHA/ESC 2006 Guidelines for the Management of Patients with AF⁹ and HRS/EHRA/ECAS Expert Consensus Statement, we recommend that AF ablation trials primarily include patients who have failed or are intolerant to at least one Vaughan-Williams¹⁰ class I or class III anti-arrhythmic drug (AAD). Depending on the study design, it may also be possible to include patients who have failed only rate control medical therapy. We also believe that for the purpose of interpreting study results, subjects with confounding characteristics should be excluded from your study. For

⁹ Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. *Circulation* 2006;114:e257-e354.

¹⁰ Vaughan Williams EM. Classification of anti-arrhythmic drugs. *Symposium on Cardiac Arrhythmias*. 1970;449-472.

example, subjects with a previous left heart ablation procedure should be excluded from your study.

8. Other Study Design Recommendations

A. Anti-Arrhythmic Drug Therapy

We recommend that all AADs except amiodarone be discontinued for at least five half-lives prior to the surgical ablation procedure to facilitate acute assessment of the ablation procedure. We also recommend that you evaluate the long-term effectiveness of the ablation procedure in the absence of AAD therapy. That is, if you reinitiate AAD therapy after the procedure, all study subjects should discontinue AAD use prior to the end of the blanking period. Alternatively, either as a primary or secondary effectiveness endpoint, it may be appropriate to evaluate the effectiveness of ablative therapy in the presence of a previously ineffective AAD therapy, as explained above. FDA considers AAD therapy to include primarily Vaughan-Williams¹⁰ Class I and Class III agents and amiodarone but not to include rate control medical therapy. FDA does not consider rate control medical therapy to be likely to affect AF recurrence and it would be appropriate to continue to administer these agents to study subjects consistent with widely accepted medical practice.

B. Anticoagulation

We recommend that you describe in detail your post-procedure anticoagulation protocols. You may elect to design your study with a pre-specified period that requires anticoagulation following the ablation procedure. Beyond such a defined period of required anticoagulation, we recommend that your protocol follow the published practice ACC/AHA/ESC 2006 Guidelines for managing patients with atrial fibrillation. These Guidelines advise treatment with anticoagulation therapy according to the patient's stroke risk rather than according to the presence or type of atrial fibrillation, as advised by the HRS/EHRA/ECAS Expert Consensus Statement. The protocol should clearly specify appropriate monitoring and documentation of anticoagulation status during the follow-up phase.

C. Non-Inferiority Versus Superiority

If the control group consists of subjects treated with a legally marketed surgical ablation device, the study may be designed to demonstrate non-inferiority or superiority. If your study hypothesis is intended to test non-inferiority, we recommend you provide an appropriate clinical justification for the non-inferiority margin that you choose. If your study hypothesis is intended to test superiority, we

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recommend you demonstrate a statistically meaningful significant improved risk/benefit profile showing improved benefit, reduced risk, or both.

D. Sample Size

We recommend that you provide a statistical justification for any sample size calculation. FDA recommends that you take into account all endpoints, primary and secondary, when calculating the sample size, especially in the circumstance where you intend to present comparisons between groups in your labeling for any secondary effectiveness endpoints. This will help to provide statistical robustness for your study endpoints. We believe that the primary safety endpoint will likely drive the sample size in most studies.

E. Follow-Up of Study Subjects

We recommend that you develop standardized protocols for outpatient follow-up visits to be conducted at 30 days, three months, and six months for longstanding persistent AF indications, additionally at nine months for persistent AF indications, and additionally at twelve months for paroxysmal AF indications. Follow-up visits should typically include documentation of symptoms and assessment of cardiac rhythm with twelve lead ECG, Holter monitoring, or other equivalent cardiac rhythm measurements. In addition, for paroxysmal and persistent AF indications, some monitoring modality should be made available to any subject who experiences symptoms indicative of AF recurrence. For evaluation of PV stenosis, the follow-up visits should include CT or MRI imaging, as appropriate.

In addition to the premarket follow-up considerations discussed above, extended, long-term postapproval studies may be appropriate for class III (premarket approval) devices to assess the stability of the treatment effect and any specific long-term safety and effectiveness concerns that arise during the premarket study. For devices for which postapproval studies are anticipated or a possibility, we recommend your study continue to follow subjects annually beyond marketing approval. In the event that FDA requires a postapproval study as a condition of the PMA approval (see 21 CFR 814.82(a)(2)), incorporating this extended follow-up in the original pivotal study will allow you to easily convert the premarket study into a postapproval study. This may free you from having to obtain new informed consent from study subjects for additional follow-up and having to recruit new subjects. In such an approach, you would obtain subject consent for five years of follow-up, but use a one year follow-up time period for purposes of gathering premarket safety and effectiveness data. Upon approval of your device, subjects who were treated with your device during the clinical investigation could be followed for a total of up to five years post-ablation as part of a post-market study without the need to seek a new informed consent for the additional follow-up period.

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The written protocol for the investigation must be scientifically sound. (21 CFR 812.25(b).) The importance of adequate and appropriate follow-up of study subjects cannot be overemphasized. Complete results obtained from effective follow-up contribute significantly to our ability to evaluate your marketing application; therefore, we recommend you make every effort to ensure that subjects participate in all scheduled post-procedure testing specified in your study protocol. Since missing data may be an issue at the time of data analysis, FDA recommends that the investigational protocol pre-specify one or more methods for handling missing data.

F. Blanking Period

A blanking period is a time interval following treatment during which success criteria are not counted for purposes of evaluating study endpoints. Since cardio-thoracic surgery in and of itself can provoke transient episodes of AF, and it is believed that these early recurrences are not indicative of longer-term success, we recommend that you employ a blanking period of three months during which the effectiveness of the device is not evaluated by arrhythmia monitoring. If a blanking period is used, it should restart after any repeat ablation procedure is performed. During the blanking period, you should monitor subjects for AF recurrence and you should record and document any AF events, but you should not consider recurrence of AF during this period as treatment failures.

G. Investigator Selection and Training

Sponsors must select investigators who are qualified by training and experience to investigate the device that is the subject of the study (21 CFR 812.43(a)). If an investigator or other site staff lack a thorough knowledge of the clinical procedures used in your study, we recommend that you provide training on the procedures. It may be appropriate to include a small number of subjects per site that will not be included in the endpoint evaluation (sometimes termed “roll-in” subjects) in order to avoid a learning curve bias.

H. Study Monitoring

Sponsors must ensure proper monitoring of the investigation (21 CFR 812.40), and the investigational plan must include the sponsor’s written procedures for monitoring the investigation and the name and address of any monitor. (21 CFR 812.25(e).) We recommend that you select experienced monitors and ensure that investigators adhere to the investigational plan. A sponsor who discovers that an investigator is not complying with the investigational plan must promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator’s participation in the investigation (21 CFR 812.46(a)). In addition, please see the Agency’s guidance entitled Guideline for the Monitoring of Clinical

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Investigations¹¹ for recommended approaches to monitoring clinical investigations involving FDA-regulated products.

¹¹ <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126400.htm>